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ORIGINAL PAPER

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Obsessive-compulsive syndromes and disorders

Significance of comorbidity with bipolar and anxiety syndromes

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Abstract *Objective* To determine the prevalence and clinical characteristics of comorbid obsessive compulsive disorders and syndromes (OCD/OCS), compared with pure OCD/OCS among adults in the community. *Method* Data were drawn from the Zurich Study, a longitudinal cohort study of 591 adults in the canton of Zurich. Comorbid OCD/OCS was compared with pure OCD/OCS groups in terms of distress, impairment, family history, suicide behavior and treatment using multivariable logistic regression analyses. *Results* OCD was significantly comorbid with bipolar I/II and minor bipolar disorders, anxiety states (GAD, repeated panic attacks) and social phobia, whereas there was no clear association between OCD and major depressive disorder or phobias other than social phobia. Results suggest that comorbid OCD/OCS is common among adults in the community, with the majority of those with OCD/OCS having at least one comorbid mood or anxiety disorder with a prevalence of 7.4% compared to 4.8% of remaining OCD/OCS. Comorbidity of OCD/OCS and anxiety states was more common among women (85.6%) and comorbidity with bipolar spectrum was more common among men (69.6%). Comorbid OCD/OCS was associated with significantly higher levels of treatment seeking, impairment, distress and suicidality compared with pure OCD/OCS. Comorbidity with bipolar disorders significantly increased the risk for alcohol abuse/dependence. *Conclusions* Comorbidity of OCD/OCS with bipolar disorder and bipolar spectrum disorders is common and very probably explains the association between OCD and depression found in other studies. The early recognition of bipolar/cyclothymic OCD/OCS may help to prevent the abuse of/dependence on alcohol.

Key words obsessive-compulsive disorder · comorbidity · bipolar disorder · anxiety disorders

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Introduction

To date, a relatively small number of studies have investigated the prevalence and comorbidity of OCD in community-based samples (Grabe et al. 2001; Hollander et al. 1996/1997; Karno et al. 1988). OCD is classified by DSM-IV as an anxiety disorder, but it is uncertain whether this is justified, and little is known about the association of OCD with mood and anxiety disorders, especially from epidemiological studies.

An association between obsessive-compulsive disorder and bipolar disorder was found by Dilsaver and White (1986) in a large extended family. This result was confirmed by Chen and Dilsaver (1995) in a reanalysis of the Epidemiological Catchment Area Study (ECA) data set: obsessive-compulsive disorders were found to be associated with a 1.7-fold increased likelihood of bipolar disorder (especially bipolar II disorder) compared with depression.

The National Comorbidity Survey (NCS) (Kessler et al. 1994) in the United States did not include OCD. In the NCS replication study Kessler et al. (2003) (personal communication of Ellen Walters 6 February 2003) found that over the lifetime OCD was much more strongly associated with bipolar disorder (OR = 9.0) than with major depressive disorder (OR = 3.4). The findings of Grabe et al. (2001) in a female sample were compatible with this trend; they found a stronger association of OCD with bipolar disorder (OR = 30.0) than with major depression (OR = 5.3).

Clinical studies on the other hand have suggested that bipolar II disorder plays an important role in OCD (Kruger et al. 2000; Perugi et al. 1997b, 2002). A recent

multicenter study of 612 OCD patients in France indicated that a dimensional definition of hypomania (score of 10 or more on the self-rated Checklist of Hypomania, HCL-20) rather than the diagnostic threshold of DSM-IV might help to identify a much larger bipolar subgroup (30 %) among OCD patients (Hantouche et al. 2003). Moreover, systematic research of 574 OCD patients identified 53 % as cyclothymic (Hantouche et al. 2002b). This study also demonstrated a higher severity of comorbid than pure OCD in terms of an early manifestation of OC symptoms (before age 16), depressive symptoms, suicide attempts, higher recurrence and problems at work. The presence of bipolar comorbidity did not seem to change the symptoms of OCD (Hantouche et al. 2003) but specific OC symptoms were more frequently found in the comorbid than in the pure OCD group. Such symptoms included: (a) obsessions: doubts, aggressive/impulsive symptoms, sexual and religious thoughts and (b) compulsions: repetitions, hoarding, confessing and asking questions, seeking reassurance. Moreover, another clinical study (Perugi et al. 1999) found bipolar OCD to be associated with social phobia, panic attacks, and alcohol abuse, unlike unipolar depressive OCD.

In a first analysis of the Zurich community cohort study, OC syndromes (OCS) were associated longitudinally (up to age 30) with depression, social phobia and agoraphobia but not with hypomania. Among women there was also an association between OCS and panic disorder (Degonda et al. 1993). Further follow-up data (up to age 41) on prevalence, course and comorbidity, published recently (Angst et al. 2004), confirmed the high prevalence of the OC spectrum.

The goal of this study is to expand available data on comorbidity using multivariable analyses in order to identify significant comorbid subgroups of OCD/OCS and compare them with pure groups of OCD/OCS in terms of clinical characteristics, distress, impairment, treatment and comorbidity with substance abuse/dependence.

Methodology

Sample and interviews were described in detail in paper I on the epidemiology of the OCD spectrum (Angst et al. 2004). The original sample of 591 subjects constitutes an age cohort, recruited at age 19/20 (M/F), representative of the Swiss population of the canton of Zurich. The cohort was prospectively studied over 20 years, up to the age 40/41 by 6 interviews carried out by trained clinical psychologists or psychiatrists applying a structured interview with additional open questions. A broad spectrum of psychiatric and somatic syndromes was assessed, including OC syndromes (OCS).

Diagnoses

OCD was defined by (a) the presence of at least 1 of 9 criterial OC symptoms of DSM-IV plus (b) significant distress (> 49 on an analogue scale [0–100]) or work impairment or impairment in other activities plus (c) the symptoms were subjectively not pleasurable or were unreasonable plus (d) they could not be suppressed.

An obsessive-compulsive syndrome (OCS) was defined by criteria (a) and (b) but distress needed only to be moderate (> 29). Criteria (c) and (d) did not have to be met.

Bipolar I disorder was diagnosed following the original definition of Dunner et al. (1976) by the presence of hospitalized mania; bipolar II disorders required the presence of a major depressive episode (DSM-III R) plus a hypomanic syndrome or hypomanic symptoms (Angst et al. 2003b). A sub-diagnostic group of minor bipolar disorder (MinBP) was included in the bipolar spectrum concept; it comprised dysthymia, minor and recurrent brief depression associated with hypomanic symptoms and, therefore, also cyclothymia (Angst et al. 2003a). Anxiety states consisted of DSM-III generalized anxiety disorder (GAD), repeated panic attacks over the last twelve months and DSM-III R phobias. The definition of substance abuse/dependence followed DSM-IV criteria. Benzodiazepine abuse was defined by regular at least weekly use over a full year.

The family history of first degree relatives was assessed in the context of the respective syndromes at the age of 28. Syndrome-related distress was measured by an analogue scale [0–100]; work impairment was assessed by yes/no and an analogue scale [0–100]. For the analyses of distress, which was assessed for each of the following: obsessive-compulsive syndrome, depression, mania, anxiety, panic, social phobia, the individual's maximum measure was taken into account. A history of suicide attempts was taken at each interview.

Statistics

Prevalence rates were weighted for the stratified sampling. OCD and OCS were estimated as a function of a set of psychopathological covariates using multivariable logistic regression analysis. Effect modifying of OCS, anxiety and bipolar syndromes was assessed using logistic regression with interaction terms. All models were estimated with STATA 8.0.

Results

Sample and prevalence rates

Table 1 presents the frequencies and prevalence rates of the syndromal groups OCD/OCS, bipolar and anxiety. We found 30 cases of OCD and 81 of OCS. There were 152 cases of bipolar spectrum syndromes and 190 cases

Table 1 Diagnoses and prevalence rates by sex

	Subjects			Prevalence rates % (95 % C. I.)			
	M + F	Males	Females	M + F	Males	Females	p
OCD	30	11	19	3.5 (1.9–6.3)	1.7 (0.6–4.8)	5.4 (2.6–10.5)	0.06
OCD and OCS	111	55	56	12.2 (9.0–16.4)	11.5 (7.4–17.6)	12.8 (8.4–19.2)	0.72
BP I/BP II	93	37	56	11.5 (8.3–15.7)	9.3 (5.5–15.3)	13.6 (9.0–20.2)	0.25
Bipolar spectrum[1]	152	65	87	20.9 (16.5–26.1)	17.1 (11.8–24.3)	24.6 (18.1–32.4)	0.13
GAD	108	45	63	14.1 (10.5–18.6)	11.6 (7.2–18.0)	16.5 (11.3–23.5)	0.23
Rep. panic attacks	121	37	84	11.0 (8.1–14.8)	3.7 (2.2–6.2)	18.1 (12.8–25.0)	0.00
Anxiety states[2]	190	70	120	21.6 (17.3–26.6)	14.3 (9.6–20.8)	28.6 (21.8–36.5)	0.00
Social phobia	84	22	62	7.6 (5.2–10.9)	4.9 (2.4–9.8)	10.2 (6.5–15.5)	0.08

[1] Bipolar I, II disorders and minor bipolar disorders; [2] Generalized anxiety disorder, repeated panic attacks

of anxiety states (repeated panic attacks, generalized anxiety disorder (GAD).

The cumulative prevalence rates across all 6 interviews were OCD 3.5 %, OCD/OCS 12.2 %, bipolar spectrum disorders 20.9 %, anxiety states 21.6 % and social phobia 7.6 %. There were no gender differences in OCS but females predominated among subjects with anxiety disorders (Table 1).

Associations of OCD/OCS with anxiety and bipolar syndromes

Logistic regression (Tables 2 and 3) demonstrated that OCD/OCS was significantly associated with the bipolar spectrum (including minor bipolar disorders), panic disorder, generalized anxiety disorder (GAD), the association with social phobia neared significance. There was no significant association, however, between OCD/OCS and major depressive disorder, depressive spectrum disorders, agoraphobia or specific phobias. On the basis of these findings we defined comorbidity by the presence of the anxiety (repeated panic attacks, GAD, social phobia) and bipolar (BP I, II, MinBP) spectra. The analyses of OCD and OCD/OCS cases gave very similar results; in order to maximize power for all further analyses, the two groups were unified and will be called OCS* (N = 111).

Fig. 1 shows the common and statistically significant overlap between OCS* and anxiety and bipolar spectrum

Table 2 Threshold and spectrum disorders: multivariable logistic regression on OCD, adjusted for sex and stratified sampling

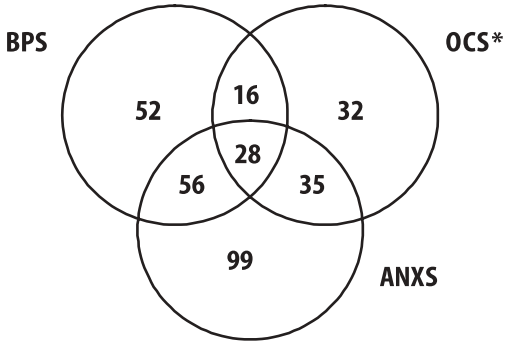
	OCD		OCD	
	OR (95 % C. I.)	p	OR (95 % C. I.)	p
Major depr. dis.	1.2 (0.4–3.3)	0.77	–	
Depr. spectrum[1]	–		1.9 (0.6–6.7)	0.30
BP I/II dis.	2.0 (0.8–5.0)	0.14	–	
BP spectrum[2]	–		3.4 (1.0–11.5)	0.05
Panic attacks	2.4 (1.1–5.6)	0.04	2.3 (1.0–5.3)	0.05
GAD	2.6 (1.2–5.9)	0.02	2.4 (1.1–5.3)	0.04
Social phobia	2.4 (1.0–5.7)	0.06	2.3 (0.9–5.2)	0.08

[1] Major depression, dysthymia, minor and recurrent brief depression; [2] Bipolar I, II disorders and minor bipolar disorders

Table 3 Threshold and spectrum disorders: multivariable logistic regression on OCS* (OCS/OCD), adjusted for sex and stratified sampling

	OCS*		OCS*	
	OR (95 % C. I.)	p	OR (95 % C. I.)	p
Major depr. dis.	1.2 (0.7–2.6)	0.50	–	
Depr. spectrum[1]	–		1.4 (0.8–2.6)	0.20
BP I/II dis.	1.6 (0.9–2.8)	0.10	–	
BP spectrum[2]	–		2.1 (1.2–3.8)	0.01
Panic attacks	1.6 (1.0–2.7)	0.07	1.5 (0.9–2.5)	0.11
GAD	2.0 (1.2–3.4)	0.006	1.9 (1.1–3.1)	0.02
Social phobia	1.6 (0.9–2.8)	0.12	1.5 (0.8–2.6)	0.18

[1] Major depression, dysthymia, minor and recurrent brief depression; [2] Bipolar I, II disorders and minor bipolar disorders



Odds Ratios: BPS * ANXS = 2.6 (1.7 – 3.8)
BPS * OCS = 1.8 (1.2 – 2.9)
ANXS * OCS = 2.4 (1.6 – 3.8)

Fig. 1 Overlap between the three syndromes: OCS/OCD (OCS*), anxiety (ANXS), BP spectrum (BPS)

disorders; 79 of 111 OCS* cases (71.2 %) were comorbid. Based on these findings, we sub-classified OCS* by presence or absence of comorbidity as shown in Table 4; up to age 41 pure OCS* was found in 4.8 % of the population, and OCS* with both anxiety and bipolar syndromes in 3.5 %, 1 % had OCS* with bipolar syndromes and 2.9 % had OCS* with anxiety disorders. The latter group showed a strong female preponderance of 85.6 % ($p < 0.001$) while pure OCS* and OCS* plus bipolar syndromes tended to be more prevalent among men (n. s.).

Family history

The more severe the comorbidity among adults with OCS*, the more likely it was that they had a positive family history of OCD (see Table 5). Adults with OCS* who suffered from both bipolar syndromes and anxiety syndromes had the highest rates of family history of OCD (17.9 %), anxiety states (53.6 %) and depression (75.9 %). In addition, all OCS* subgroups had elevated rates of a family history of alcohol abuse/dependence (17.9 to 28.6 %) compared to controls (8.2 %) ($\chi^2 = 4.71$, $df = 1$, $p < 0.03$).

Consequences of comorbidity

Table 6 presents mean distress scores for comorbid and pure OCS*, bipolar and anxiety syndromes, rates of lifetime treatment, impairment and history of suicide attempts. Distress from OCS was independent of comorbidity. But patients with comorbid OCS* were more severely affected than adults with pure OCS*, with a 2- to 3-fold higher likelihood of lifetime treatment, significantly higher overall distress and up to ten-fold higher suicidality, compared with pure OCS*. It is remarkable that the rate of suicide attempts associated with pure OCS* (3.1 %) did not differ from that among control subjects (2.3 %). The consequences for OCS* subjects with comorbid anxiety disorders vs comorbid bipolar disorder were comparable, with the exception of treatment rates, which were slightly higher in the bipolar subgroup of OCS*.

Finally it is interesting to note that the group with OC symptoms was also clinically relevant. It consisted of 51 % comorbid cases (66/130), with high suicide attempt and treatment rates and distress scores.

Comorbidity with substance abuse/dependence

A major feature of comorbidity was *substance abuse and dependence*. Table 7 demonstrates that comorbidity of OCS* with bipolar syndromes was significantly associated with substance abuse and especially with alcohol abuse/dependence. Pure OCS*, however, was not associated with higher substance abuse rates than mood disorders, but both tended to be higher than controls. The same was true for pure bipolar vs. depressive mood dis-

Table 4 Comorbid subgroups of OCS* (including OCD)

	Contr.	Mood disord.	OC sympt.	OCS* "pure"	OCS* + Anx	OCS* + BP	OCS* + BP + Anx	p (χ^2)
Subjects (N)	142	208	130	32	35	16	28	
Women %	43.0	57.2	48.5	25.0	68.6	50.0	57.1	0.002
Weighted prevalence (m + f) %	35.6 (30.0–41.6)	34.6 (29.1–40.5)	17.7 (13.6–22.6)	4.8 (2.8–8.1)	2.9 (1.6–5.3)	1.0 (0.4–2.5)	3.5 (1.9–6.3)	
Weighted prevalence women %	42.2 (32.3–52.8)	60.3 (50.0–69.7)	47.3 (34.0–61.0)	39.5 (17.4–66.8)	85.6 (70.5–93.6)	30.4 (9.5–64.5)	52.2 (24.1–79.0)	0.028

Table 5 Family history of OC spectrum

	Contr. (1)	Mood (2)	OCsx (3)	OCS* "pure" (4)	OCS* + Anx (5)	OCS* + BP (6)	OCS* + BP + Anx (7)	p (χ^2) 1 vs (4–7)	p (χ^2) 4 vs (5–7)
N	142	208	130	32	35	16	28	–	
Family history	%	%	%	%	%	%	%	–	
OCD	1.9	2.0	3.7	0.0	8.8	6.3	17.9	0.03	0.07
Anxiety/Panic	12.0	29.3	26.2	31.3	42.9	37.5	53.6	0.0005	0.17
Depression	30.2	52.8	55.1	46.2	55.9	56.3	75.9	0.0005	0.14
Mania	5.0	10.4	7.1	4.8	3.0	21.4	7.1	0.53	0.61
Alcohol	8.2	18.6	20.9	20.0	19.4	28.6	17.9	0.03	0.96
Sedatives	16.4	11.6	15.4	6.7	12.9	7.1	14.3	0.35	0.53

Table 6 Consequences of comorbidity of OCS* (including OCD)

	Contr. (1)	Mood (2)	OCsx (3)	OCS* "pure" (4)	OCS* + Anx (5)	OCS* + BP (6)	OCS* + Anx + BP (7)	p[a] 1 vs (4–7)	p[a] 4 vs (5–7)
N	142	208	130	32	35	16	28		
Distress OC (mean)	0	0	0	38.3	38.9	46.9	39.3	0.0001	0.81
Overall distress (mean)	56.0	85.1	79.0	72.9	88.5	86.3	93.9	0.0001	0.0001
Treatment (%)	17.6	54.3	50.8	31.3	65.7	81.3	89.3	0.0005	0.0005
Work imp. (%)	47.2	89.4	85.4	78.1	97.1	100.0	100.0	0.0005	0.0005
Any imp. (%)	62.7	98.6	90.8	87.5	100.0	100.0	100.0	0.0005	0.001
Suicide attempts (%)	2.3	13.9	15.4	3.1	17.1	18.8	32.1	0.0005	0.013

[a] Kruskal-Wallis test for means, χ^2 test for frequencies

Table 7 Association with substance abuse/dependence

	Contr. (1)	Mood (2)	Ocsx (3)	OCS* "pure" (4)	OCS* + Anx (5)	OCS* + BP (6)	OCS* + Anx + BP (7)	p (χ^2) 1 vs (4–7)	p (χ^2) 4 vs (5–7)
N	142	208	130	32	35	16	28		
	%	%	%	%	%	%	%		
Substance	18.3	30.8	31.5	31.3	11.4	50.0	50.0	0.01	0.87
Alcohol	16.2	22.1	25.4	18.8	2.9	37.5	35.7	0.36	0.74
Drugs	7.0	12.5	12.3	9.4	2.9	25.0	17.9	0.20	0.63
Benzos	0.7	7.2	4.6	6.3	8.6	0.0	14.3	0.003	0.65

orders without OC symptoms/diagnoses: depressive spectrum disorders without hypomanic symptoms and controls had similar comorbidity with alcohol abuse/dependence (13.9 % and 15.4 % respectively), whereas pure bipolar spectrum disorders showed a double risk (31.6 %) ($chi^2 = 8.89, df = 1, p < 0.01$). Additional separate analyses by gender did not change the results.

Applying multivariable logistic regression analyses to OCS* comorbid with bipolar disorder as the dependent variable and adjusting for gender and stratified sampling we found strong associations with alcohol (OR = 3.6; 95 % C. I. 2.3–5.5) and drug abuse (OR = 1.8; 95 % C. I. 1.1–3.1). In contrast, OCS* comorbid with anxiety was associated with low rates of alcohol and drug abuse compared to controls; however, the presence of anxiety was associated with regular benzodiazepine use. There were no specific interactions in the reported associations.

Discussion

Our prospective cohort study comprised a relatively small community sample, which was enriched by high scorers on the Symptom Check List 90 R (Derogatis 1977). It included 30 patients with OCD and 81 patients with OCS (prevalence rates 3.5 % and 8.7 % respectively), all of whom were observed longitudinally from the ages of 20 to 41.

For the investigation of comorbidity, important modifications were made to some conventional diagnostic criteria: on the basis of their genetic validity (Angst et al. 2003b) bipolar II disorders were defined broadly and included patients with major depressive episodes (DSM-III-R) with two or more hypomanic symptoms (Angst et al. 2003b). Using this scheme, half of all major depressives were diagnosed as bipolar-II disorders. Panic was defined as repeated panic attacks, GAD by DSM-III criteria and phobias by DSM-III-R criteria. Comorbidity was defined restrictively: only syndromes significantly associated (on the basis of multivariable logistic regressions) with OCD and OCS were taken into account.

We found associations between OCS* and bipolar disorder (mainly BP-II), anxiety (panic and GAD) and social phobia; in contrast to two other epidemiological studies (Grabe et al. 2001; Karno et al. 1988) we found no associations with major depressive disorders. The latter findings are compatible with several other studies, which stressed the importance of BP disorders in OCD comorbidity (Chen and Dilsaver 1995; Hantouche et al. 2002a, 2003; Kruger et al. 1995; Perugi et al. 1997a, 1999). We assume that our wide definition of BP II disorders reduced the habitual over-diagnosis of major depressive disorders (MDD) so far that the co-occurrence of OCS* with pure MDD became negligible. A lack of association between OCS* and depression was also confirmed by our analyses of depressive spectra (including bipolar and unipolar dysthymia, minor and recurrent brief depression). This negative finding is consistent with results of another analysis in the Zurich study, which showed that a broad definition of BP-II disorders shifted the alcohol comorbidity from major depression to bipolar-II

disorder (Angst et al. in preparation). OCS* is also common in soft bipolar conditions, such as bipolar-II disorder, brief recurrent hypomania or cyclothymic temperament, as shown by a French study conducted in collaboration with the AFTOC (French Association of OCD patients) (Hantouche et al. 2002a).

The associations between OCS* and anxiety disorders (panic, GAD, social phobia) came as no surprise in light of earlier reports on the associations between OCD and (a) GAD and panic disorder (Perugi et al. 1997a, 1999) and (b) social phobia (Karno et al. 1988; Grabe et al. 2001; Rasmussen and Eisen 1990, 1992).

Unlike previous studies on comorbidity, we sub-classified OCS subjects into several categories: (a) OCS with double comorbidity (bipolar *and* anxiety disorders) as distinct from OCS with simple comorbidity, (b) with bipolar *or* (c) with anxiety disorders, (d) pure OCS* cases and (e) controls (without mood disorders) in order to compare the clinical relevance in terms of prevalence rates, clinical characteristics, family history and substance abuse/dependence. As in other studies, the comorbid groups were more seriously ill as compared with pure OCS, illustrated by distress scores and impairment, treatment and suicide attempt rates. These results confirm those of the French study of Hantouche et al. (2003), who found that the suicide attempt rate in cyclothymic OCD was almost double (20 %) the rate (12 %) in the non-cyclothymic OCD group. This rate of 20 % is very similar to our finding of 18.8 % in the sub-group of OCS and bipolar syndromes. However, when OCS* presented with double comorbidity (bipolar and anxiety) the suicide attempt rate increased to 32.1 %, and other indicators also showed this condition to be more serious than single comorbidity.

The type of comorbidity (bipolar, anxiety) had little impact on measures of severity of OCS*; however, it significantly influenced the associations with alcohol abuse/dependence and drug abuse. The link between substance abuse and bipolar comorbidity in OCD has already been suggested by Italian patient data (Perugi et al. 1999).

Substance abuse was clearly more frequent in bipolar OC groups but not elevated in anxious OC groups. In fact, there was a trend toward less substance (but not benzodiazepines) abuse in OC cases with anxiety compared to controls.

The finding that subjects with double comorbidity also had higher rates of positive family histories for OCS and other disorders (depression, mania, anxiety, panic) was surprising; this may suggest that associated genetic liabilities for mood, anxiety and OC syndromes could play a role in comorbidity. A similar finding was reported from a French study where cyclothymic OCD patients showed higher rates of a family history for suicide attempts and chronic psychiatric conditions (Hantouche et al. 2003) than pure OCD patients.

Conclusions

Comorbidity of OCS* with both bipolar and anxiety disorders is linked with higher severity and especially higher treatment rates than simple forms of comorbidity with either condition. In addition, bipolar comorbidity increased and anxious comorbidity decreased the risk of substance abuse/dependence (alcohol and drugs). This classification by comorbidity could be taken into account in research on and treatment of OCD/OCS. Bipolar OCD should be treated with combined treatment of mood stabilizers and antidepressants.

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